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Eosinophilic asthma and the role of monoclonal antibodies

Abstract: Eosinophilic asthma presents with continuous airway inflammation resistant to inhaled corticosteroids but responsive to oral glucocorticoids and monoclonal antibodies. Diagnostic criteria include significantly elevated blood or sputum eosinophils and/or fractional exhaled nitric oxide. Five monoclonal antibodies are used for treatment, with accurate diagnosis and early intervention essential to better outcomes.

By Lynda Jarrell, DNP, APRN, FNP-BC, CNE

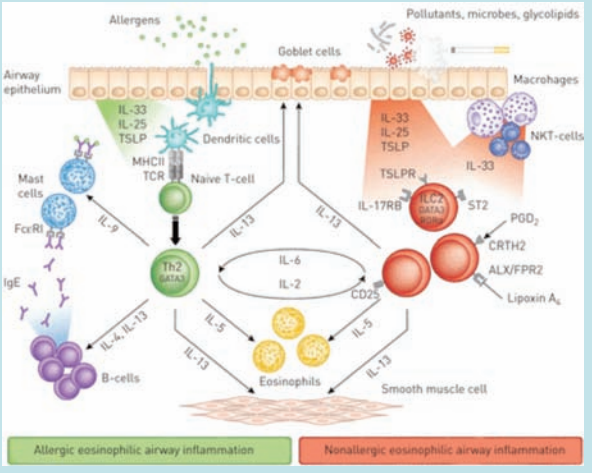
Asthma has been recognized relatively recently as a collection of different phenotypes which may have similar manifestations but disparate pathologies. Eosinophilic asthma (EA) is a phenotype typically with adult onset that has poorer outcomes than other types of asthma. Despite treatment with inhaled corticosteroids (ICS), EA continues to cause airway inflammation. It is resistant to ICS but responsive to oral glucocorticoids and monoclonal antibodies (mAbs).[1] EA can be allergic or nonallergic, and even though the cytokine cascade is somewhat different between the two, inflammatory responses result in the same airway hyperreactivity, and diagnosis and treatment are the same.

EA and the role of mAbs

Early diagnosis is vital for effective treatment of EA with mAbs, which are safer than long-term oral

Keywords: antibodies, biologics, eosinophilic asthma, eosinophils, monoclonal antibodies

Allergic and nonallergic eosinophilic airway inflammation[5]



Allergic and nonallergic pathways to eosinophilic airway inflammation in asthma. CRTH2: chemoattractant receptor homologous molecule expressed on Th2 cells. ALX/FPR2: receptor for lipoxin A4. FcεRI: high-affinity receptor for IgE. GATA3: GATA-binding protein 3. PG: prostaglandin. ROR: retinoic acid receptor-related orphan receptor. NK: natural killer. MHC: major histocompatibility complex. TCR: T-cell receptor.

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glucocorticoids.[2] NPs must understand the role of eosinophils in asthma, recognize signs and symptoms, and be familiar with these medications to manage patient expectations for treatment referral to asthma/immunology or pulmonary specialists.[3]

The role of eosinophils in asthma

Eosinophils are granulocytes originating in the bone marrow that play a vital role in both allergic and nonallergic asthma in adults. Differences in the cytokine cascade between allergic and nonallergic asthma represent two different trigger pathways. In allergic asthma, dendritic cells direct allergens to the cluster of differentiated (CD4) T cells, including T-helper cells that generate interleukin (IL)-5 and IL-13 and trigger immunoglobulin E (IgE) swapping in B cells, airway eosinophilia, and mucus hypersecretion. In nonallergic EA, air pollutants, microbes, and glycolipids trigger the release of IL-33, IL-25, and thymic stromal lymphopoietin. These trigger lymphoid cells that produce significant amounts of IL-5 and IL-13, triggering eosinophilia, mucus hypersecretion, and airway hyperreactivity (see *Allergic and nonallergic eosinophilic airway inflammation*).[2,4-6]

Eosinophils can cause airway hyperresponsiveness and release of highly charged basic proteins with cytotoxic effects, leading to lung tissue damage. Cell damage triggers hyperplasia of fibroblasts, airway smooth muscle, and goblet cells, as well as extracellular matrix deposition, which causes airway remodeling associated with a rapid decline in lung function.[2,7]

Diagnosis of EA

Early detection and diagnosis of adult-onset asthma are vital, but identification is not always clear-cut. Control is challenging due to exacerbating factors, complex drug treatment regimens, and decreased patient quality of life.[1,2] Recommendations by the Global Initiative for Asthma (GINA), American Thoracic Society (ATS), and European Respiratory Society (ERS) first established EA diagnosis.[3,7] If suspected, treatment for comorbidities should be initiated and adherence and inhaler technique assessed before the diagnosis of severe uncontrolled asthma unresponsive to treatment is made.[3]

EA is characterized by significantly elevated eosinophils in blood (≥150/mcL) and/or sputum (≥2%); elevated fractional concentration of exhaled nitric oxide ([FeNO] ≥20 parts per billion [ppb]), and/or allergen-driven clinical presentation.[3] FeNO is used as a noninvasive biomarker for asthmatic inflammation and the test to measure it is quick, easy, and noninvasive. For the test, the patient blows into a handheld device that tracks results. It is usually done in a physician's office, and the test results are available right away.[8-10]

Most patients experience more than two exacerbations annually with typical onset at age 25-35. These patients are often not allergic to common allergens and are at high risk for exacerbations, but are resistant to ICS; however, oral glucocorticoids and anti-IL-5 treatments are effective. Resulting respiratory issues include decreased forced expiratory volume per second (FEV_1), continuous airflow limitation unresponsive to bronchodilators, air trapping, and lung hyperinflation.[1-3]

Diagnostic indicators (blood eosinophils, sputum eosinophils, and FeNO) can be altered by oral corticosteroids and should be measured for initial assessment before starting treatment if possible, but do not determine biologic treatment eligibility. If inconclusive, blood eosinophils and FeNO should be measured up to three times in order to diagnose EA.[3]

Sputum analysis is the optimal diagnostic test for EA, but relies on labs with trained staff and is not available in all clinical practices.[4] A systematic review and meta-analysis of alternative testing methods including peripheral blood eosinophils, FeNO, and serum IgE showed only moderate diagnostic accuracy.[8] Westerhof et al. reported that blood eosinophils and FeNO had equal diagnostic veracity in finding sputum eosinophilia in smoking and nonsmoking adults with asthma, with both more predictive than serum IgE.[2,9] FeNo >50 ppb is significant in adults and >35 ppb is significant in children.[10] Values of blood eosinophils <90/mcL (<0.09x10^9/L) indicated lack of respiratory eosinophilia in 92% of patients, and ≥410/mcL (≥0.41x10^9/L) indicated ≥3% eosinophils present in sputum of 95% of patients.[2,9]

Blood eosinophil testing is easily accessible in clinical practice and represents the best means of early and accurate diagnosis.[2,3,11] A persistent relationship exists between blood and sputum eosinophilia, and elevated blood eosinophil counts ≥3x10^9/L are correlated with severe symptoms, recurrent exacerbations, and poor prognosis.[2,12,13] Ideal use of biomarkers in clinical practice remains controversial, and the number of tests required to diagnose EA and the role of other biomarkers such as FeNO, serum periostin, and dipeptidyl peptidase-4 remains unclear. Consequently, a combination of biomarkers may be needed to validate EA diagnosis.[8]

Treatment

Beginning only recently, five mAbs are currently used for the treatment of EA—all targeting cytokines in the inflammatory cascade (see *mAbs used in the treatment of EA*).[14,15] GINA recommends use of mAbs in symptomatic patients or patients with exacerbations who are taking high-dose ICS and long-acting beta agonists and who have allergic or eosinophilic biomarkers or need maintenance oral glucocorticoids.[3] Patients in endemic areas or at risk for parasitic infection should be tested and treated before beginning mAb therapy.[6] These medications may diminish the immune response against parasitic infections.

Omalizumab is a humanized anti-IgE antibody that has a strong affinity to the Fc portion of IgE molecules and binds to free IgE, thereby decreasing unbound IgE levels and inhibiting binding to FcεRI. This prevents degranulation of mast cells and hinders the release of inflammatory mediators.[16,17] Omalizumab is administered by subcutaneous injection and does not require renal or hepatic dosing adjustments; however, a boxed warning has been issued for anaphylaxis.[16,17]

Omalizumab has been shown to reduce fall asthma exacerbations in children that are secondary to viral infections.[18] A 2019 systematic review concluded that short-term omalizumab use is effective in adolescents and adults with severe allergic asthma and presented solid evidence of long-term effectiveness for up to 4 years, with developing evidence of effectiveness beyond 4 years. The study established that long-term omalizumab use decreases exacerbations, increases asthma control, improves lung function and quality of life, reduces overall medication use, and decreases hospital visits.[19]

Mepolizumab, a humanized mAb, prevents activation and survival of eosinophils by binding IL-5 and preventing it from binding to the α-chain of IL-5 eosinophil surface receptors.[12,20-22] Previously available only in a lyophilized formulation that required administration by a healthcare professional, mepolizumab is now supplied in a prefilled autoinjector syringe and can be administered at home by the patient or caregiver.[20] Studies have concluded that patients prefer self-administered injections—particularly using autoinjectors—and find them easy to use.[20] Mepolizumab does not require dosing adjustments for renal or hepatic impairment and no boxed warning has been issued, but there is a precaution for hypersensitivity reactions and annual review of the treatment is recommended.[13,17,20]

Five trials have investigated mepolizumab efficacy, all including patients with at least two exacerbations annually while receiving high-dosage ICS.[21] Four trials included patients with blood or sputum eosinophilia.[21-26] Exacerbations were reduced by 53% with subcutaneous mepolizumab, and I.V. delivery reduced exacerbations by 47%-48% at low dose, 39% at medium dose, and 49%-52% at high dose.[21-23,25] Chupp et al. reported significant reduction of clinically significant exacerbations, as well as significant reduction of exacerbations requiring hospitalization or ED visits.[21,24]

Reslizumab has the same mechanism of action as mepolizumab.[13,17,21,27] Reslizumab is administered by I.V. infusion. No renal or hepatic dosing adjustments are required; however, a boxed warning has been issued for anaphylaxis and annual review of treatment is recommended.[13,17]

mAbs used in the treatment of EA[13,15,17,46-50]

Drug	Indication	Select Warnings/Precautions and Adverse Reactions*	How Supplied/Cost
Omalizumab	Moderate-to-severe persistent asthma in patients age 6 years and older: • with a positive skin or lab test to a perennial aeroallergen, and • inadequate symptom control with ICS	Headache, nausea, injection site irritation, eosinophilia with vasculitis Boxed warning for anaphylaxis	Supplied in prefilled syringes of 75 mg/0.5 mL or 150 mg/1 mL and as lyophilized powder (150 mg) in vial for reconstitution Reconstituted solution (150 mg each)/$1,354.18. Prefilled syringe is $677.09/75 mg dose $1,354.18/150 mg dose
Mepolizumab	Approved as add-on maintenance therapy for patients with severe asthma age 6 years and older and with an eosinophilic phenotype	Hypersensitivity reactions including anaphylactic reaction, headache, injection site reaction, back pain, fatigue	Supplied in a prefilled autoinjector, prefilled syringe, or vial for reconstitution. Vial for reconstitution (100 mg each), autoinjector or prefilled syringe 100 mg cost is $3,688.90.
Reslizumab	Add-on treatment in adults with severe asthma and with an eosinophilic phenotype	Anaphylactic reaction (boxed warning), oropharyngeal pain	Supplied as 100 mg/10 mL vial for preparation as a weight-based I.V. infusion. Vials cost $111.84 per mL.
Benralizumab	Add-on maintenance treatment in patients age 12 years and older with severe asthma and with an eosinophilic phenotype	Hypersensitivity reaction including anaphylactic reaction, headache, pharyngitis	Supplied as prefilled syringe or autoinjector pen, $6,052.46 for the prefilled syringe and the autoinjector
Dupilumab	Add-on maintenance treatment in patients age 12 years and older with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid-dependent asthma	Hypersensitivity reactions including anaphylaxis, eosinophilia with vasculitis or pneumonia (rare), conjunctivitis and keratitis	Supplied as prefilled pen or syringe. $933.03 per mL for the pen-injector and the prefilled syringe 300 mg/2 mL. $1636.89 per mL for the prefilled syringe 200 mg/1.14 mL

*Note: Not all warnings, precautions, or adverse reactions are listed. Please refer to drug labels for complete information.

A systematic review by Edris et al. found that four trials have explored the effectiveness of reslizumab in diverse patient populations; however, due to differences in inclusion criteria, the studies are not directly comparable.[21] In a randomized, phase II, placebo-controlled study, Castro et al. concluded that reslizumab significantly reduced sputum eosinophils and improved airway function and that there was a trend toward improved asthma control compared with a placebo.[28] The study included patients with uncontrolled asthma on high-dose ICS and sputum eosinophils of ≥3%. Two phase III trials had different inclusion criteria and did not consider past exacerbations, complicating comparison of results.[29,30] In 2015, Castro et al. reported results from two multicenter, parallel, double-blind, randomized, placebo-controlled, phase III trials affirming that reslizumab significantly reduced asthma exacerbations compared with placebo.[31] Reslizumab was also found to be effective in delaying onset of the first exacerbation in patients with EA.[21]

Benralizumab binds to IL-5 receptors of eosinophils and basophils causing cell death.[13,17] Benralizumab may be self-administered. No renal or hepatic dosing adjustments are required and no boxed warning has been issued; however, there is a precaution for hypersensitivity and annual treatment reviews are recommended.[13,17]

In three phase II and three phase III trials, benralizumab decreased blood eosinophil counts and improved exacerbation rates.[21,32-37] Bleecker et al. and FitzGerald et al. observed exacerbation rates 36%-45% lower than placebo with 30 mg benralizumab administered every 4 weeks.[35,36] Park et al. affirmed a 33% reduction with 2 mg, 45% reduction with 20 mg, and 36% reduction with 100 mg benralizumab every

4 weeks for the first three doses and every 8 weeks thereafter.[32] Data from studies by Castro et al. and Bleecker et al. was inconclusive with respect to the effectiveness of benralizumab in reducing ED visits or hospital admissions.[21,34,35] Nowak et al. reported a reduction of 49% in exacerbation rates and 60% in exacerbation-related hospitalizations.[33]

Dupilumab inhibits IL-4 and IL-13 signaling, decreasing release of inflammatory cytokines and IgE.[13,17] This mAb may be self-administered. Renal or hepatic dosing adjustments are not required and no boxed warnings have been issued; however, there are precautions for hypersensitivity reactions and annual treatment review is recommended.[13,17]

A large-scale phase III trial (LIBERTY ASTHMA QUEST) that included patients with uncontrolled asthma and at least one exacerbation within the previous year despite treatment with high-dose ICS showed reduction of exacerbations by 46%-47.7% when dupilumab 200 or 300 mg was given every 2 weeks and a phase IIb trial with similar inclusion criteria found reductions of 70%-71% with that dosing schedule.[21,38,39] Patients with elevated blood eosinophils or higher FeNO exhibited even greater reductions.[21,38]

Safety

Long-term safety profiles have not yet been established because use of mAbs for treatment of EA is a relatively recent development. Two published open-label extensions of reslizumab and mepolizumab trials, respectively, reported that despite good overall safety profiles, there were more reported adverse reactions for both drugs than placebo.[40,41] Adverse reactions occurred in 71% of patients receiving reslizumab.[41] Frequent adverse reactions were worsening of asthma and nasopharyngitis. Serious adverse reactions affected 78 of 1,051 (7%) patients, and 18 of 1,051 (2%) discontinued treatment because of adverse reactions. Fifteen of 1,023 (1%) had various malignancies. Malignancies were not an exclusion and five of the patients had a history of malignancy. No clinical significance was seen between reslizumab versus placebo patients. Patients on reslizumab maintained improved lung function and asthma control and blood eosinophil counts were seen to decline to pretreatment counts after reslizumab termination. Castro et al. showed a lower rate of adverse reactions in patients on dupilumab than the placebo group.[38] In a 2015 meta-analysis, Lai et al. concluded that the safety profile of omalizumab was favorable but noted the lack of data beyond 52 weeks.[42] A study combining data from the Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO) trial and Benralizumab, an anti-interleukin-5 receptor α mAb, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA) trials found benralizumab safe and supported long-term use in patients with uncontrolled severe asthma.[35,36,43]

Biologics are expensive and should be reserved for patients with the greatest potential benefit.

Other mAbs

Tezepelumab is in phase III trials to confirm or discredit efficacy in the treatment of EA after early trials produced promising results.[21] Lebrikizumab, tralokinumab, GSK679586, and MEDI-528 have been shown to have no effects or minimal effects on outcomes of severe EA.[21] Daclizumab was removed from the market because of adverse events.[21]

Cost

Biologics are expensive and should be reserved for patients with the greatest potential benefit, raising a potential disparity issue for low-income and uninsured patients. Most insurance companies cover at least partial cost of these medications with confirmed diagnosis of severe asthma.[44] Two studies have reported that without significant discounts in drug costs, neither omalizumab nor mepolizumab are cost effective.[44,45]

Summary

EA is a phenotype typically with adult onset, poorer outcomes, and greater severity than other types of asthma. Patients present with continuous airway inflammation resistant to ICS but responsive to mAbs.[1] NPs must understand the role of eosinophils in asthma, recognize the signs and symptoms of EA, and make accurate diagnoses to treat patients appropriately.

EA is clinically driven by allergens not common in childhood asthma and characterized by elevated blood (≥150/mcL) and/or sputum (≥2%) eosinophils, or elevated FeNO (≥20 ppb) levels.[3] Most patients experience more than two exacerbations per year with typical onset at age 25-35. They are not allergic to common allergens, are at high risk for exacerbations, and are resistant to ICS, but can be successfully treated with oral glucocorticoids and mAbs.[1-3] mAbs have been shown overall to be safe and effective in the treatment of severe EA. Research is needed to clarify asthma, compare biologics to support selection of the best medication option for each patient, and determine long-term safety of the individual drugs.[21] Treatment with biologics is expensive and should be prescribed only for patients with the greatest potential benefit (for example, those that remain symptomatic or have frequent exacerbations with high-dose ICS or those that require oral glucocorticoids).

Primary care NPs must be knowledgeable about signs and symptoms of EA and available medications to be able to manage patient expectations and make the appropriate treatment referrals.[3] NP

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- Read the article. The test for this CE activity is to be taken online at **www.nursingcenter.com/CE/NP**. Tests can no longer be mailed or faxed.
- You'll need to create (it's free!) and log in to your personal CE Planner account before taking online tests. Your planner will keep track of all your Lippincott Professional Development online CE activities for you.
- There's only one correct answer for each question. A passing score for this test is 7 correct answers. If you pass, you can print your certificate of earned contact hours and access the answer key. If you fail, you have the option of taking the test again at no additional cost.
- For questions, contact Lippincott Professional Development: 1-800-787-8985.
- Registration deadline is March 3, 2023.

PROVIDER ACCREDITATION

Lippincott Professional Development will award 2.0 contact hours and 1.0 pharmacology contact hour for this continuing nursing education activity.

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